

# **SERUM FIBRINOGEN LEVELS IN** **ACUTE ISCHEMIC STROKE**



**The Tamilnadu Dr. M.G.R. Medical University**

**SERUM FIBRINOGEN LEVELS IN ACUTE**  
**ISCHEMIC STROKE**

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**CERTIFICATE**

This is to certify that this dissertation “**Serum Fibrinogen Levels in Acute Ischemic Stroke**” is a bonafide work done by **Dr.Karthik pandian.K.S.** in the Department of Medicine **PSG Institute of Medical Sciences and Research**, Coimbatore under my supervision and guidance.

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## **INTRODUCTION :**

**Many prospective epidemiological studies have reported positive associations between the risk of cardiovascular disease and plasma fibrinogen levels[1] Fibrinogen is the major coagulation protein in blood by mass, the precursor of fibrin, and an important determinant of blood viscosity**

and platelet aggregation.[2,3] Because fibrinogen levels can be reduced considerably by lifestyle interventions that also affect levels of established risk factors (such as regular exercise, smoking cessation, and moderate alcohol consumption), there is interest in the possibility that measurement (or modification) of fibrinogen may help in disease prediction or prevention[4].

Nevertheless, the relationship between hyperfibrinogenemia, atherosclerosis and thrombosis is complicated. As the process of thrombogenesis is very closely related to atheroma formation (atherogenesis), it follows that specific thrombogenic factors such as fibrinogen may play key roles in the process of atherosclerotic lesion formation, with subsequent effects on cardiovascular diseases . However, knowledge about the precise determinants of plasma fibrinogen levels in health and disease is as yet incomplete, and many paradoxes are still present. For example, it is known that plasma fibrinogen is higher in Black than in White patients [5] but (in the UK at least) coronary artery disease is less common in Blacks than in White patients,

while hypertension and stroke are conversely more common [6,7]. Plasma fibrinogen is also influenced by many factors: it increases with age, body mass index, smoking, diabetes and post menopause and is related to fasting serum insulin, low-density-lipoprotein (LDL) cholesterol lipoprotein(a) and leukocyte count. Conversely, it decreases with moderate alcohol intake, physical activity, increased high-density-lipoprotein (HDL) cholesterol, and with hormone replacement therapy [8,9,10] .

## **Fibrinogen and fibrin structure and functions;**

Fibrinogen molecules are comprised of two sets of disulfide-bridged Aalpha-, Bbeta-, and gamma-chains. Each molecule contains two outer D domains connected to a central E domain by a coiled-coil segment. Fibrin is formed after thrombin cleavage of fibrinopeptide A (FPA) from fibrinogen Aalpha-chains, thus initiating fibrin polymerization. Double-stranded fibrils form through end-to-middle domain (D:E) associations, and concomitant lateral fibril associations and branching create a clot network. Fibrin assembly

facilitates intermolecular antiparallel C-terminal alignment of gamma-chain pairs, which are then covalently 'cross-linked' by factor XIII ('plasma protransglutaminase') or XIIIa to form 'gamma-dimers'. In addition to its primary role of providing scaffolding for the intravascular thrombus and also accounting for important clot viscoelastic properties, fibrin(ogen) participates in other biologic functions involving unique binding sites, some of which become exposed as a consequence of fibrin formation. This review provides details about fibrinogen and fibrin structure, and correlates this information with biological functions that include: (i) suppression of plasma factor XIII-mediated cross-linking activity in blood by binding the factor XIII A2B2 complex. (ii) Non-substrate thrombin binding to fibrin, termed antithrombin I (AT-I), which down-regulates thrombin generation in clotting blood. (iii) Tissue-type plasminogen activator (tPA)-stimulated plasminogen activation by fibrin that results from formation of a ternary tPA-plasminogen-fibrin complex. Binding of inhibitors such as alpha2-antiplasmin, plasminogen activator

inhibitor-2, lipoprotein(a), or histidine-rich glycoprotein, impairs plasminogen activation. (iv) Enhanced interactions with the extracellular matrix by binding of fibronectin to fibrin(ogen). (v) Molecular and cellular interactions of fibrin beta15-42. This sequence binds to heparin and mediates platelet and endothelial cell spreading, fibroblast proliferation, and capillary tube formation. Interactions between beta15-42 and vascular endothelial (VE)-cadherin, an endothelial cell receptor, also promote capillary tube formation and angiogenesis. These activities are enhanced by binding of growth factors like fibroblast growth factor-2 (FGF-2) and vascular endothelial growth factor (VEGF), and cytokines like interleukin (IL)-1. (vi) Fibrinogen binding to the platelet alpha(IIb)beta3 receptor, which is important for incorporating platelets into a developing thrombus. (vii) Leukocyte binding to fibrin(ogen) via integrin alpha(M)beta2 (Mac-1), which is a high affinity receptor on stimulated monocytes and neutrophils [11].



## **AIM OF THE STUDY ;**

**Fibrinogen is a major determinant of plasma viscosity; an elevated fibrinogen level might also be associated with cardiovascular events.**

**Whether the association between fibrinogen and cardiovascular events and**

whether fibrinogen predicts incidence of ischemic stroke is unclear. The aim of the study is to evaluate the fibrinogen levels in 50 patients with ischemic stroke and to determine the consistency of its association when compared with 50 patients without stroke as controls.

## **REVIEW OF LITERATURE ;**

The associations between fibrinogen level and the incidence of a broad range of different chronic diseases are particularly striking, including not just major ischemic cardiovascular diseases but also the aggregate of nonvascular mortality [12,13]. The magnitude of the associations persisted largely unchanged in analyses restricted to never smokers and to disease cases

recorded several years after the baseline examination, reducing the likelihood that they were mainly due to cigarette smoking habits and/or early cardiovascular disease. It has been suggested that such associations reflect a response to cumulative environmental stressors (as indicated by circulating levels of fibrinogen and other inflammatory factors), which may modify the risk, progression, and outcomes of various chronic diseases [14]. Although the lack of specificity in the associations of fibrinogen level with different vascular and nonvascular outcomes does not necessarily exclude a causative role for fibrinogen in ischemic cardiovascular diseases, there remains scope in these estimates for biases due to residual (or unmeasured) confounding by other factors.

## **Pathophysiology ;**

Fibrinogen is a soluble glycoprotein found in the plasma, with a molecular weight of 340 kDa [15]. It comprises of three pairs of non-identical polypeptide chains (alpha, beta and gamma chains) [16] linked to each other

by disulphide bonds. Fibrinogen has a biological half-life of about 100 h and is synthesized predominantly in the liver [17]. As a clotting factor, fibrinogen is an essential component of the blood coagulation system, being the precursor of fibrin. However, at the 'usual' plasma levels of 1.5 to 4.5 g/l, its concentration far exceeds the minimum concentration of 0.5–1 g/l necessary for haemostasis.

Fibrinogen plays a vital role in a number of physiopathological processes in the body, including inflammation, atherogenesis and thrombogenesis. Nevertheless, our understanding of the mechanisms leading to the atherothrombogenic action of fibrinogen is fragmentary. Proposed mechanisms include the infiltration of the vessel wall by fibrinogen, haemorrheological effects due to increase in blood viscosity, increased platelet aggregation and thrombus formation. Furthermore, plasma fibrinogen is also a prominent acute-phase reactant. It augments the degranulation of platelets in response to adenosine diphosphate (ADP), when taken up by the  $\alpha$ granules. Thus, elevated

concentrations of fibrinogen, perhaps secondary to inflammation or infection (*Chlamydia pneumoniae* or *Helicobacter pylori*) implicated in cardiovascular risk may operate, in part, by increasing the reactivity of platelets.[18]

## **Fibrinogen and inflammation ;**

The process of inflammation is primarily mediated by its interaction with leucocytes through the surface receptors of the latter termed 'integrins'. The 2 main receptors for fibrinogen on the surface of leukocytes include Mac-1 (CD11b/CD18, alpha M beta 2) and alpha X beta 2 (CD11c/CD18, p150, 95). Leukocytes (both monocytes and myelocytes) can specifically induce MAC-1 receptor to bind fibrinogen [19,20]. The ability of MAC-1 receptor to bind fibrinogen results from the maturational changes occurring in the receptor during the process of cell differentiation, and is not seen in a resting leucocyte. The site on fibrinogen that interacts with MAC-1 is not shared by other integrins.[21]

Fibrinogen is also a ligand for Intercellular Adhesion Molecule-1 (ICAM-

1), and enhances monocyte-endothelial cell interaction by bridging the Mac-1 on monocytes to ICAM-1 on endothelial cells.[22,23] Thus, ICAM-1 behaves as cell surface ligand for alpha L beta 2 and alpha M beta 2 (MAC-1) integrins, and has a key role in leukocyte adhesion to the vascular endothelium. Furthermore, fibrinogen upregulates and increases the concentration of ICAM-1 proteins on the surface of endothelial cells, resulting in increased adhesion of leukocytes on the surface of endothelial cells [24] ,even at high shear rates in flow conditions [25]. Moreover, the fibrinogen binding to ICAM-1 on the endothelial cells also mediates the adhesion of platelets. The interaction of fibrinogen and cells expressing ICAM-1 is associated with cellular proliferation [26].

Fibrinogen, on binding to its integrin receptor on the surface of leukocytes also facilitates a chemotactic response, thus playing a vital role in the process of inflammation [27]. One of the proposed mechanisms by which fibrinogen induces pro-inflammatory changes in leukocytes includes an increase in the free intracellular calcium and increased expression of neutrophil

activation markers. These processes result in an increase in phagocytosis, antibody-mediated leucocyte toxicity and delay in apoptosis [28].

Fibrinogen is also involved in the facilitation of both cell–cell interaction and the interaction of cell and extracellular matrix such as collagen [19,29].

Thus, as explained above, fibrinogen is an important mediator of cell–cell interaction, adhesion and inflammation.

Finally, there is evidence that fibrinogen facilitates the biomaterial-provoked inflammatory response [30]. Interaction with the biomaterial results in conformational changes within the fibrinogen molecule and conversion into ‘proinflammatory’ fibrinogen, resulting in the exposure of the epitope that interacts with the MAC-1 receptor for macrophages [30,31].

## **Fibrinogen and atherogenesis ;**

There seems to be little doubt that fibrin deposition can both initiate atherogenesis and contribute to the growth of plaques [32,33]. Fibrinogen and its metabolites appear to cause endothelial damage and dysfunction by a

number of mechanisms [34]. Many human atherosclerotic lesions, showing no evidence of fissure or ulceration, can contain a large amount of fibrin, which may either be in the form of mural thrombus on the intact surface of the plaque, in layers within the fibrous cap, in the lipid-rich core, or diffusely distributed throughout the plaque. This phenomenon may be compounded by the decrease in arterial intimal fibrinolytic activity and plasminogen concentration observed in cardiovascular disease [32].

It has been proposed that once in the arterial intima, fibrin stimulates cell proliferation by providing a scaffold along which cells migrate, and by binding fibronectin, which stimulates cell migration and adhesion [35].

Fibrin degradation products, which are present in the intima, may stimulate mitogenesis and collagen synthesis, attract leukocytes, and alter endothelial permeability and vascular tone. In the advanced plaque, fibrin itself may be involved in the tight binding of LDL and accumulation of lipid, resulting in the lipid core of atherosclerotic lesions [32]. However, it cannot be



overemphasized that many of these observations are only *associations*, and a definite *causal* role for fibrinogen cannot be fully demonstrated.

## Fibrinogen and thrombogenesis ;

Thrombogenesis is regulated by a fine balance between the coagulation and fibrinolytic pathways. Subsequent to vessel wall trauma, tissue thromboplastin is released from the sub-endothelium. Tissue thromboplastin in turn triggers the *extrinsic pathway* of coagulation by activating factor VII to VIIa. Contact of blood with the foreign surface initiates the *intrinsic pathway* of coagulation, by activating factor XII to XIIa, as well as platelets. Platelet aggregation, however, does not confer adequate stability, and therefore activation of the coagulation pathway is also necessary.

The final common pathway of the coagulation cascade involves the activation of factor X to Xa, and the subsequent activation of prothrombin to thrombin. Thrombin, which is a protease enzyme, facilitates the cleavage of

fibrinogen into fibrin monomers, which link to each other both sideways and end-to-end to form fibrin polymers. Activated factor XIII facilitates the cross linkage of fibrin polymers to form a stable fibrin clot.

Fibrinogen is also involved in the final common pathway of platelet aggregation. Fibrinogen cross-links the platelets by binding the glycoprotein IIb-IIIa receptor on the platelet surface [36]. This has become more relevant with the advent of glycoprotein IIb-IIIa receptor inhibitors, which block this final common pathway of platelet binding.

## Determinants of plasma fibrinogen levels;

Factors associated with raised fibrinogen levels.

Factors associated with lower fibrinogen levels.

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Advancing age

Young age

Female sex

Male sex

**Black race**

**Caucasians**

**Smoking**

**Cessation of smoking**

**Obesity**

**Weight reduction**

**Physical inactivity**

**Regular exercise**

**Elevated cholesterol**

**Moderate alcohol consumption**

**Menopause**

**Hormone replacement therapy**

**Oral contraception**

**Low socio-economic status**

**Stress**

**Plasma fibrinogen level is dependent upon both genetic and environmental factors.**

## **Genetic influences;**

**The evidence suggests that plasma fibrinogen levels are probably under substantial genetic control, as genetic polymorphisms account for some 20–**

51% of variations in plasma fibrinogen levels [37,38]. The demonstration of such substantial genetic control further supports the view that plasma fibrinogen is a primary risk factor for atherothrombotic disorder rather than just a reflection of such disorder.

The fibrinogen locus comprises three genes coding for fibrinogen gamma (FGG), fibrinogen alpha (FGA), and fibrinogen beta (FGB), clustered in a region of approximately 50 kb on the long arm of chromosome 4q23-q32, the direction of transcription of the  $\beta$  gene being in the opposite direction to that of the other two [39]. There is a single copy of each gene; the  $\alpha$  gene in the middle flanked by the  $\beta$  gene on one side and the  $\gamma$  gene on the other. Variation in the fibrinogen locus contributes to the individual differences in plasma fibrinogen levels [40]. However, the precise molecular mechanism(s) underlying the genetic heritability of plasma fibrinogen concentration remain unclear.

The genetic influence on the fibrinogen beta-chain gene has been more extensively studied, because  $\beta$ -chain synthesis is the limiting step in the

production of mature fibrinogen [41]. In recent years, several polymorphisms have been identified in the fibrinogen chain genes that determine plasma levels of fibrinogen, mainly by restriction fragment length polymorphism (RFLP) and single-stranded conformation polymorphism (SSCP) analyses [40,42,43]. For example, the BclI RFLP of the  $\beta$  fibrinogen gene is associated with between-person differences in plasma fibrinogen levels [44]. Similarly, van't Hooft *et al.* [45] demonstrated that the -455G/A and -854G/A polymorphisms of the  $\beta$  fibrinogen gene have a significant impact on the plasma fibrinogen concentration. The -455G/A mutation in the promoter region of the  $\beta$  fibrinogen gene is one of the strongest genetic variations, associated with an increase in plasma fibrinogen in both genders in the general population [43,46]

However, the results have been conflicting, and some studies have failed to demonstrate such relationships between these genetic polymorphisms and plasma fibrinogen levels. For example, Connor *et al* [47] found that plasma fibrinogen levels did not show any significant associations with the four

fibrinogen polymorphisms examined, at the  $\alpha$  (*TaqI*),  $\beta$  (*BclI* and *HaeIII*), and  $\gamma$  (*KpnI* / *SacI*) fibrinogen loci. Humphries *et al.* [37] found that the individuals with the genotype B1B1 had a mean fibrinogen of 2.74 g/l, while those with B2B2 had a mean plasma fibrinogen level of 3.69 g/l, a level previously associated with a strongly increased risk of IHD. Those heterozygous for the two alleles, with the genotype B1B2, had mean plasma fibrinogen levels of 2.98 g/l.

Despite the recognition that plasma fibrinogen levels are under a 'significant' degree of genetic control, the precise genes/alleles/polymorphisms that are responsible for the variation in levels between different populations, and the clinical significance, if any, still remains uncertain as much of the limited data are conflicting.

## Extrinsic influences ;

There is evidence that plasma fibrinogen level and its associated cardiovascular risk may be dependent upon an interaction between

environmental and intrinsic (genetic) factors rather than just the latter. For example, there is a dose-response effect between the number of cigarettes smoked and plasma fibrinogen level, as well as an inverse relationship with time since cessation of smoking [48]. Moderate drinking may lower plasma fibrinogen concentration, and if fibrinogen is a causal risk factor for cardiovascular disease, it may be one of the variables that explain the protective effect of moderate alcohol consumption on cardiovascular disease[49]. The observation of extrinsic influences on plasma fibrinogen levels suggests that elevated plasma fibrinogen levels may be modifiable through appropriate lifestyle changes. Furthermore, there is evidence that strategies that lower the cardiovascular risk may also lower plasma fibrinogen levels[50].

Nonetheless, whether these measures translate to clinically relevant benefits remain uncertain, as the mediator(s) of the beneficial effects may be due to mechanisms (e.g. endothelial function, lipids, etc.), or combinations of mechanisms, other than the reduction of plasma fibrinogen *per se*. Some of the

more important extrinsic influences on plasma fibrinogen levels are discussed below.

## **Gender ;**

The second World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Augsburg survey found the crude fibrinogen values to be consistently higher in women than in men of all ages, irrespective of pregnancy or the use of oral contraceptives [51,52,53,54,55]. Plasma fibrinogen levels are higher in women than in men, even after accounting for confounding factors, as observed in the Goteborg MONICA survey. Furthermore, this pattern was observed even among healthy adolescents in the Florence Teenager Study [52]. However, occasional studies have failed to demonstrate a significant gender difference in plasma fibrinogen levels between men and women [53]. It should also be noted that amongst the prospective epidemiological studies, only the Framingham study included women; thus the influence of plasma fibrinogen on cardiovascular risk amongst



women still needs to be more strongly established.

## **Age ;**

Plasma concentrations of fibrinogen generally increase with age [56,57].

This age-related increase in plasma fibrinogen may be due to a slower rate of disposal of fibrinogen, rather than an increased production rate [58].

## **Body mass index and body habitus ;**

Plasma fibrinogen concentration has been positively correlated with body mass index, the waist circumference, the hip circumference and waist-to-hip ratio in both sexes [59]. Indeed, plasma fibrinogen level is significantly higher amongst patients with a body mass index of  $> 30 \text{ kg/m}^2$ , compared to those with body mass index  $< 25 \text{ kg/m}^2$  [60], and rises with higher quartiles of skin fold thickness [61].

Moreover, weight reduction can reduce plasma fibrinogen. For example, Ditschuneit *et al* [59]. reported that in patients who were extremely overweight and had high plasma fibrinogen levels, a reduction in weight (mean

$\pm$  SEM  $20 \pm 3$  kg) correlated with a decrease in plasma fibrinogen levels ( $0.33 \pm 0.1$  g/l). Surgical treatment of morbid obesity may have a long-term beneficial effect on mortality from cardiovascular and thromboembolic disease, as demonstrated by the reduction of the decrease in prothrombotic factors, including fibrinogen [62]. In a study by Primrose *et al* [62], haemostatic and fibrinolytic factors were measured before and again 6 and 12 months after surgery (vertical gastric stapling with or without jejuno-ileal bypass) in 19 patients suffering from morbid obesity. This resulted in a mean decrease in body weight of 64 kg at 12 months, accompanied at 12 months by significant reductions in median concentrations of serum cholesterol (from 5.3 mmol/l to 3.6 mmol/l); factor VII (from 113% of normal to 99%); fibrinogen (from 3.5 g/l to 2.8 g/l); and plasminogen activator inhibitor-1 activity (from 21 IU/ml to 6.3 IU/ml).

## Metabolic syndrome ;

'Metabolic syndrome' is characterized by the presence of three or more of

the following metabolic markers: high-density lipoprotein-cholesterol  $< 1.13$  mmol/l; triglycerides  $\geq 1.80$  mmol/l; glucose  $\geq 5.5$  mmol/l; diastolic blood pressure  $\geq 90$  mm Hg. Obesity, poor cardiorespiratory fitness and the metabolic syndrome are all closely linked to each other. Furthermore, these may be related to the development of haemorrheological abnormalities (such as increased fibrinogen) associated with the metabolic syndrome. Plasma fibrinogen increases with a number of components of the metabolic syndrome, independent of major confounders [63]. The age-adjusted OR for hyperfibrinogenaemia ( $\geq 3.47$  g/l) was non-significantly higher at 1.69 (95% CI 0.87–3.27;  $p = 0.119$ ) for subjects with the metabolic syndrome when compared with those with no metabolic abnormalities [61].

## Physical exercise ;

### *Acute exercise*

Changes in the plasma fibrinogen levels have been reported after acute exercise, especially when post-exercise raw data were corrected for the

contraction of plasma volume [64]. However, the results reported from various studies have been conflicting, due to differences in the populations studied, exercise protocols, testing procedures, and the analytical methods used for the assessment of plasma fibrinogen [65,66]. Moreover, whether exercise-induced blood hypercoagulability *in vitro* corresponds to *in vivo* thrombin generation and fibrin formation is unknown.

Acute exercise may cause a rise in plasma fibrinogen levels in patients with some vascular disease states. For example, in patients with chronic AF exercised to exhaustion, plasma fibrinogen rose significantly within 20 minutes with a simultaneous alteration in fibrinolytic activity (i.e., reduced PAI) [67]. In another study, in patients with stable chronic heart failure exercised to exhaustion, plasma fibrinogen level increased significantly within 20 minutes [68]. These observations may contribute to the thromboembolic risk associated with these disease states.

***Regular exercise ;***

Regular exercise over a span of few weeks or months has shown a reduction in plasma fibrinogen levels both in healthy and diseased individuals.

In healthy individuals, strenuous exercise over a period of 4 weeks lowers plasma fibrinogen levels, equivalent to a difference of about 15% in the risk of IHD [69]. In one study, a 12-week exercise-training programme in patients with mild hypertension resulted in a significant decrease in plasma fibrinogen and an improvement in overall coronary risk profile [65]. Regular physical exercise may also be beneficial in reducing overall coronary risk profile by decreasing the blood pressure and plasma fibrinogen levels in otherwise healthy individuals; Nevertheless, plasma fibrinogen levels return to baseline values after resumption of sedentary activity [70].

Furthermore, in the Caerphilly Prospective Heart Disease Study [71], plasma fibrinogen concentrations were lowered by 0.24 g/l in the third of men who were the most active in leisure activities. Overall, the average decrease achieved by regular endurance exercise over several months was around 0.4

g/l [72]. Men with low level of social activities and activities at home had a higher plasma fibrinogen concentration, when compared to those with high levels of activity [73].

Therefore, the available evidence would suggest that regular exercise over a period could exert its beneficial influence on cardiovascular events through a beneficial effect on plasma fibrinogen levels.

## Seasonal differences ;

Cardiovascular disorders, cerebrovascular disorders, associated risk factors and mortality all show a seasonal variation, with a peak during winter season, especially among the elderly. Correspondingly, plasma fibrinogen levels show a seasonal variation, with the peak in winter, both in normal healthy adults and in patients with cardiovascular disorders [74-78]. For example, the Rotterdam Study found a seasonal difference of 0.34 g/l (95% CI 0.29–0.39) and the difference was more pronounced in subjects aged 75 years or older[78]. In the latter group, the difference between winter and the summer

months ranged as high as 23% [75].

Seasonal variation in plasma fibrinogen levels with a rise in winter could be due partly to the observed seasonal variations in the known vascular risk factors, and partly to the factors described below.

## **Vitamin C and infection ;**

It has been suggested that a lower dietary intake of vitamin C and/or an increase in upper respiratory infections (with its associated acute phase response) in the winter seasons might be the underlying cause for the raised levels of acute-phase reactants, especially fibrinogen. Furthermore, plasma fibrinogen levels correlate with various markers of respiratory infection, such as neutrophil count, C-reactive protein, self-reported cough and coryza[79]. However, the studies have generally yielded inconsistent results [79-82].

An increase in dietary vitamin C of 60 mg/day was associated with a decrease in plasma fibrinogen concentrations of 0.15 g/l, equivalent to a decline of approximately 10% in risk of IHD [80]. Nonetheless, it remains to be

seen as to whether treatment of the infections results in decrease in plasma fibrinogen levels and whether decreasing the fibrinogen levels results in decreased cardiovascular morbidity and mortality.

Organisms such as *Chlamydia pneumoniae* and *Helicobacter pylori* are implicated in the pathogenesis of coronary artery disease [83,84]. Fibrinogen may be implicated in the complex interaction of these infectious agents and coronary artery disease. Antibodies to *C. pneumoniae* are significantly increased in patients with stroke and severe essential hypertension, but there was no apparent association between these titres and plasma fibrinogen levels [82]. Fibrinogen is also thought to be an intermediary in the apparent link between *H. pylori* infection and coronary artery disease but once again, studies have yielded inconsistent results [84,85]. The recent STAMINA (South Thames Trial of Antibiotics in Myocardial Infarction and Unstable Angina) study showed that although antibiotic treatment failed to reduce plasma fibrinogen levels significantly, it significantly reduced adverse cardiac events in patients



with acute coronary syndromes; however, the effect was independent of *H. pylori* or *C. pneumoniae* seropositivity [86]. Furthermore, in a recent meta-analysis of all published prospective studies, *C. pneumoniae* antibody titres were not predictive of CHD in the general population [87]. Therefore, the question of whether these infections increase the cardiovascular risk and if so, whether fibrinogen is an intermediary, is still far from clear.

## **Psychosocial factors ;**

Adult plasma fibrinogen concentration is determined by various factors operating throughout life. The available data suggest that the inverse relation between socio-economic status and coronary artery disease may be partly explained by differences in plasma fibrinogen levels.

In a cross-sectional study of civil servants in London, aged 45–55 years, measures of childhood environment (adult height, father's social class, and participant's education) were inversely associated with adult plasma fibrinogen concentration in both sexes [88]. Lower socio-economic status (as shown by

employment grade) was also associated with higher plasma fibrinogen concentrations, which were not accounted for by measures of childhood circumstances. Control over work, assessed by personnel managers and self, was also inversely related to plasma fibrinogen levels [88].

Furthermore, the results of the Stockholm Heart Epidemiology Programme (SHEEP) study suggest that adverse job characteristics might also be related to plasma fibrinogen concentrations, particularly in female workers [89]. Low self reported control over the job, inferred high demand, and inferred job strain were significantly associated with increased plasma fibrinogen concentration.

## **Hormonal status ;**

Both cross sectional and longitudinal studies demonstrate that oral contraceptive (OC) pill use results in a significant rise in plasma fibrinogen levels, an effect that seems to be strongest in OCs with a high oestrogen concentration [90]. Furthermore, there are positive and significant interactions

between OC use and smoking in their effects on haemostatic variables, including fibrinogen [91]. Conversely, plasma fibrinogen level returns to normal on discontinuation of the OC pill, usually within about 3 months [92].

Both the menopausal status and HRT have independent effects on plasma fibrinogen levels [93]. The increases in factor VII C, fibrinogen, and cholesterol levels with the menopause would increase the risk of fatal IHD in postmenopausal women by about 40%, compared with the risk in premenopausal women of the same age [94]. However, lower plasma viscosity and plasma fibrinogen levels are found in women on HRT (both with oestrogen-progesterone combinations and oestrogen monotherapy) [95]. Theoretically therefore, the use of HRT may exert a protective effect by reducing plasma fibrinogen levels.

However, evidence for the influence of menopause and/or HRT on plasma fibrinogen has not been unequivocal. For example, Conard *et al.* (1997) reported a significant increase in plasma fibrinogen levels with oral oestrogen

HRT [96]. Moreover, the only study on the effect of HRT on haemostatic factors following surgical menopause (patients aged  $43 \pm 6.5$  years) did not find any significant difference in the levels of plasma fibrinogen among patients, prior to the surgery and following oophorectomy while taking HRT.

Interestingly, in the Postmenopausal Estrogen/Progestin Interventions (PEPI) study, which was a three-year, double-blind, placebo-controlled trial of HRT on risk factors in 875 postmenopausal women, a lower baseline plasma fibrinogen level was significantly associated with venous thromboembolic events among subjects who subsequently received HRT [97].

Many questions relating to the interaction between hormonal status, fibrinogen and cardiovascular disorders remain unanswered. The available data are inconsistent, and vary with regard to populations and type of hormone preparation studied.

## **Smoking ;**

Available evidence suggests that cigarette smoking is strongly associated

with increased plasma fibrinogen levels, and the adverse cardiovascular effects of smoking may partly be mediated through an increase in plasma fibrinogen levels [98-100]. Indeed, each cigarette smoked per day increases mean plasma fibrinogen by 0.35 g/l. [53]

Similar data are available from epidemiological studies. In the Framingham study, plasma fibrinogen values were significantly higher in smokers than in non-smokers, with a dose-dependent increase with smoking in both sexes; ex-smokers had values as low as those of non-smokers. Over 10 years of follow-up, the risk in both sexes increased progressively in relation to antecedent plasma fibrinogen values over the 1.8–4.5 g/l range [101]. In the second MONICA Augsburg survey, the impact on the population plasma fibrinogen level was most pronounced for age in both sexes, followed closely by body mass index and cigarette smoking [51]. In the MUNSTER Heart Study, smoking-related adverse changes in plasma fibrinogen were of greater magnitude in men than in women [102]. A switch from cigarette to cigar

smoking is also associated with a large increase in plasma fibrinogen levels [103], in keeping with the observation that cigar smokers remain at an increased risk of IHD. [104]

Passive smoking is not free of risk either, and may increase the risk of coronary heart disease partly by increasing plasma fibrinogen concentrations [105]. On average, plasma fibrinogen concentrations were 0.86 g/l higher in women exposed to cigarette smoke outside the home and 1.12 g/l higher in women exposed both in and outside the home, when compared to women unexposed in either location. Thus, these effects of passive smoking were about 40–60% of that of current active smoking. Furthermore, smoking could have an acute effect on plasma fibrinogen levels. For example, post-MI patients who smoked within the previous 24 h had significantly higher plasma fibrinogen levels than patients who refrained from smoking for 24 h. [106]

How does smoking alter plasma fibrinogen levels? Smoking results in an inflammatory reaction, probably of the pulmonary bronchi and alveoli and the

blood vessels of the lung parenchyma, as evidenced by an increase in the levels of C-reactive protein [107,108]. The resulting inflammation may increase the production of the cytokines, such as interleukin-6 [109], which have major roles in the regulation of synthesis in the liver of acute-phase proteins, including fibrinogen [110,111]. Thus increased plasma fibrinogen levels in smokers may reflect a chronic inflammatory state of the vascular wall, and may act as an intermediary in the enhanced coronary risk among smokers.[112]

Smoking potentiates thrombosis at the dysfunctional endothelium, at least partly by increasing the concentration of plasma fibrinogen and altering the activity of platelets. All these pro-atherogenic effects of smoking to injure the endothelium are also observed, albeit to lesser extent, in passive smokers. [113]

## **Alcohol ;**

Moderate drinking appears to lower plasma fibrinogen concentrations. The so-called 'French paradox' may be at least partly explained in relation to

the effects of alcohol on clotting factors. For example, in the DESIR Study (Data from an Epidemiological Study on the Insulin Resistance syndrome) of 4967 men and women aged 30–64 years, alcohol consumption was associated with plasma fibrinogen levels, with higher concentrations in those who were non-drinkers or who drank > 60 g of alcohol per day. This U-shaped association was stronger amongst men than women. Consumption of wine and spirits was also associated with changes in plasma fibrinogen levels, whereas consumption of beer or cider was not. In women, for example, 1 g of alcohol per day induces a 0.008 g/l decrease in the mean plasma fibrinogen, while in men the decrease was 0.004 g/l within the down slope of the U-shaped curve. [53]

These findings are further supported by other studies. For example, a U-shaped relation between alcohol consumption and plasma fibrinogen levels was also found in the second MONICA Augsburg survey (1989–1990), especially amongst men [51]. In the Scottish Heart Health Study, plasma



fibrinogen was negatively associated with alcohol consumption in both sexes [114]. Nevertheless, as with other factors, there have been occasional reports of failure to correlate alcohol with plasma fibrinogen, as in the Munster Arteriosclerosis Study (MAS). [57]

The precise mechanisms by which alcohol influences plasma fibrinogen levels remain uncertain. Animal experiments have suggested that alcohol exerts its effects through the action on the genetic expression of plasma fibrinogen in the liver cells [115]. On the other hand, alcohol can also result in high blood pressure and atrial fibrillation (AF), which are conditions associated with high plasma fibrinogen levels. [116,117]

## **Fibrinogen and CAD ;**

The concentration of plasma fibrinogen positively correlated with the severity of the underlying coronary heart disease in some studies [118-120]. Plasma fibrinogen levels are higher in patients with unstable angina than in patients with stable angina, and higher in patients with severe vasospastic

angina than in those with mild vasospastic angina and stable effort  
angina.[121,122]

Nevertheless, a more recent study by Hoffmeister *et al.* failed to  
demonstrate a relationship between plasma fibrinogen levels and the severity  
of IHD in any of the three systems used to score the severity. [123]

Furthermore, raised plasma fibrinogen levels have prognostic  
implications, being a strong predictor of coronary heart disease, fatal or non-  
fatal, new or recurrent, and of death from an unspecified cause, for both men  
and women [124-126], and therefore, a predictor of accelerated coronary  
atherosclerosis. Furthermore, the beneficial effect of statins and fibrates in  
reducing coronary artery diseases events and mortality cannot entirely be  
explained by their beneficial effect on lipids. In addition to lipid lowering, the  
modification of thrombus formation and degradation, alteration in  
inflammatory response, plaque stabilization and improved endothelial function  
are thought to be responsible for additional reduction of morbidity and

mortality due to cardiovascular events [127]. Nonetheless, as explained below, although statins appear to improve thrombogenicity and endothelial dependent vasoresponsiveness, there is lack of convincing evidence of a reduction in plasma fibrinogen levels with statins, in contrast to the fibrates. For example, in the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT), the beneficial effect of bezafibrate on coronary events in young male survivors of MI, was attributed partly to the reduction in plasma fibrinogen levels, in addition to the beneficial effect on plasma lipid profile. [128]

Fibrinogen is also associated with other well-known risk factors for cardiovascular disease, such as smoking, age, obesity, hypertension and diabetes [129]. Elevation of plasma fibrinogen levels may therefore provide a mechanism for the risk factors to exert their effect. Certainly, the positive association between plasma fibrinogen levels and cardiovascular events is as strong as that for elevated cholesterol levels [130]. Higher levels of plasma fibrinogen markedly increase the predictive power of high serum LDL

cholesterol; conversely, low plasma fibrinogen levels are associated with low coronary risk, even when LDL is raised [131]. Interestingly, plasma fibrinogen levels are also raised in people with family history of premature heart disease. Therefore, modification of cardiovascular risk factors may result in beneficial reduction of plasma fibrinogen levels and better cardiovascular outcome.

## **FIBRINOGEN AND STROKE ;**

Several epidemiological studies have provided prospective data on plasma fibrinogen levels in relation to cardiovascular disease. According to these studies, the risk of developing a cardiovascular event such as IHD or stroke is 1.8 to 4.1 times higher in subjects with fibrinogen levels in the top third than in those with levels in the lower third. Preliminary evidence also suggests that reducing fibrinogen levels in patients with high baseline levels and coronary disease may be beneficial.

A meta-analysis of the six prospective epidemiological studies with samples representative of the general population, concluded that plasma

fibrinogen was an independent cardiovascular risk factor, the results being uniform despite the diversity of study designs, sample compositions, follow-ups and end-point criteria. In this meta-analysis of 92 147 person-years experience, all prospective studies showed that plasma fibrinogen was associated with subsequent myocardial infarction (MI) or stroke. The odds ratio for the events in the upper vs. lower tertile varied between 1.8 (95% CI 1.2–2.5) in the Framingham study and 4.1 (95% CI 2.3–6.9) in the Gottingen risk incidence and prevalence study, with a summary odds ratio of 2.3 (95% CI 1.9–2.8).

In another meta-analysis, which included 22 studies (13 prospective, 5 cross-sectional, and 4 case-control) trying to determine the role of fibrinogen as a cardiovascular risk factor, the overall estimate of risk of cardiovascular events in subjects with plasma fibrinogen levels in the higher tertile, was twice as high as that of subjects in the lower tertile (OR 1.99; 95% CI 1.85–2.13). High plasma fibrinogen levels were associated with an increased risk of cardiovascular disease in healthy as much as in high-risk individuals.

## **Fibrinogen Is a Marker for Nephropathy and Peripheral Vascular Disease in Type 1 Diabetes ;**

Fibrinogen levels were associated with nephropathy status in type 1

diabetic subjects. In men but not women, there was a significant correlation between fibrinogen levels and albumin excretion rate across the entire range of albumin loss, with no evidence of a threshold for increased fibrinogen. In women, discontinuous analysis demonstrated that, whereas fibrinogen levels were similar in normoalbuminuric and microalbuminuric subgroups, there was a significant increase in plasma fibrinogen with macroalbuminuria. Therefore, in both men and women, fibrinogen was related to nephropathy as manifested by the severity of albuminuria. The results of previous studies in diabetic subjects have not been consistent and have shown varying associations between the presence of micro- and/or macroalbuminuria and elevated fibrinogen concentrations, most probably as a result of the varying influence of multiple additional factors and drug treatments. It is not clear, however, whether hyperfibrinogenemia occurs secondary to the onset of nephropathy or is a primary factor that antedates microalbuminuria. Further prospective evidence is required to confirm hyperfibrinogenemia as an independent

**predictor of future diabetic nephropathy. [132]**

## **Fibrinogen as an acute-phase reactant ;**

**Plasma fibrinogen is an acute-phase protein, and is therefore likely to increase with inflammation or tissue necrosis. Interpretation of raised fibrinogen may be complicated by its behavior as an acute-phase reactant. For example, plasma fibrinogen concentrations are raised after acute stroke [133] and acute MI [134], probably as an acute phase response. Nevertheless, measurement of plasma fibrinogen levels could potentially be more useful than those of other acute phase reactants such as C-reactive protein, as fibrinogen is probably more specific to vascular disease.**

**However, plasma fibrinogen strongly predicts cardiovascular events in patients with established atherosclerotic vascular disorders. Furthermore, it is raised even before the onset of acute stroke and acute MI in patients with transient ischaemic attack [135,136] and chronic stable angina pectoris [137] respectively. Therefore, though plasma fibrinogen is raised in the context of**

acute cerebrovascular and cardiovascular events, chronically raised plasma fibrinogen appears to be an independent risk factor for these events.

## **Genetic variation in plasma fibrinogen ;**

Genetic variation in the fibrinogen gene may have implications in prognosis of patients with vascular disorders [138]. For example, the data from the Edinburgh Artery Study provide evidence that a polymorphism of the P fibrinogen gene is associated with a varying risk of peripheral atherosclerosis: the -455AA genotype was associated with over twice the risk of PAD, compared with the -455GG genotype.[139]

Furthermore, in subjects with AF, Thr312Ala polymorphism gives rise to an increased susceptibility for embolization of intra-atrial clot, and there was decreased survival in those possessing the A allele following stroke, Similarly, in some patients with deep venous thrombosis, variations in the fibrinogen genotype could predispose to the embolization of formed fibrin clot, resulting in pulmonary embolism. [140]



It is important to appreciate that although several studies demonstrate a strong association between polymorphisms of the fibrinogen  $\beta$ -chain gene and plasma fibrinogen concentration, only a few have found a direct association between the former and the risk of ischaemic heart disease. A substantial number of studies failed to find an association between polymorphisms in the fibrinogen gene and cardiovascular risk [141-143]. For example, van der Bom *et al.* found that the -455G/A polymorphism was associated with increased plasma fibrinogen levels, but not with an increased risk for MI. These findings indicate that an increased plasma fibrinogen level due to this genetic factor may not increase the risk for MI. Similarly, Doggen *et al.* found that the *TaqI*, *HaeIII* and *BclI* polymorphisms in the fibrinogen gene were not associated with MI. [141]

Therefore, many questions remain unanswered. Does a particular genetic polymorphism predispose to atherosclerotic disease? And if it does, is it mediated through raised fibrinogen or some associated mechanism? Some

studies conducted on twins suggest that the environment, rather than genetic influences could have a greater influence on plasma fibrinogen levels. [144]

## **Plasma Fibrinogen Levels in Lung Cancer ;**

In respect to the biological action of IL-6 in cancer patients, its direct effects on cancer cells have been observed [145,146], a tumor-bearing state, however, the indirect function through the host inflammatory response cannot be disregarded. Among the acute-phase proteins induced by IL-6, fibrinogen been reported to be elevated in the plasma of patients with advanced cancer [147] involved in the growth of tumor tissue [149] as well as the inhibition of the cell-mediated immune response to cancer cells [150]. Fibrinogen levels, like IL-6 levels, were found to be elevated particularly in patients with advanced squamous cell or large cell carcinoma. Although the reason why no strong correlation was found between levels of IL-6 and fibrinogen remains undetermined, it may be concerned in part with the preferential elevations of FDP level found in patients with elevated levels of both IL-6 and fibrinogen.

This corresponds precisely to the observations that plasma fibrinogen metabolism at the advanced stage of patients with solid cancer is diversely accelerated in both phases of production and degradable conversion to insoluble fibrin[147-149].

## **FIBRINOGEN AND HYPERTENSION ;**

In the Blue Mountains cohort of older Australians, in cross-sectional analysis, found that elevated plasma fibrinogen level was positively associated with prevalent hypertension both among men and women. In contrast, in prospective analysis, elevated plasma fibrinogen level was positively associated with 5-year incident hypertension among men but not women. This association was independent of smoking, alcohol intake, BMI, and other related factors. Among men, the OR of incident hypertension increased in a dose-dependent manner with increasing plasma fibrinogen and the association was consistently present in subgroup analyses stratified by smoking, BMI, and JNC7 BP categories. The findings from this long-term follow-up study of older,

community-dwelling Australians are consistent with the recent observation reported by Folsom et al [151] suggesting a moderate positive association between plasma fibrinogen and incident hypertension among men but not among women in a middle-aged, biracial US cohort [152].

## **Fibrinogen and lipoprotein (a) ;**

A correlation between Fib and Lp(a) was not evident in smokers. This observation is not unexpected, because smoking increases the plasma levels of Fib [153,154] but does not influence serum Lp(a) [155,156].. The relationship between Fib and Lp(a) levels is indeed complex. It has been proposed that more than 90% of the variability in serum Lp(a) levels is genetically determined, [157] whereas this percentage is lower (30% to 50%) for Fib [158,159]. Nevertheless, impaired renal function, the menopause, and hypothyroidism can raise serum Lp(a) levels. Fibrinogen levels are higher in smokers, obese individuals, diabetic patients, and in women, especially after the menopause. Fibrinogen levels also rise with age. We eliminated some of

this variability by considering subgroups and by excluding patients with diabetes, hypothyroidism, or impaired renal function and women taking hormone replacement therapy. And it propose that more extensive subclinical asymptomatic atherosclerosis tends to develop in subjects with largely genetically determined raised serum levels of Lp(a). This sequence of events may result in higher plasma Fib levels as a result of the inflammatory response associated with atherosclerosis [157]. This mechanism may, in part, account for the relationship between Fib and Lp(a). This hypothesis is supported by observation that the circulating levels of Lp(a) correlate with the extent of CVD;. Furthermore, the Fib–Lp(a) relationship may be influenced by a decrease in fibrinolytic activity caused by Lp(a). [157]

## **Interventions to decrease plasma fibrinogen levels**

### **Beneficial**

**Cessation of smoking**

**Medication: fibrates, doxazosin**

**Plasmapheresis**

**Moderate alcohol consumption**

### **May be beneficial**

**Weight loss**

**Lowering blood pressure**

**Hormone replacement therapy**

### **Not beneficial**

**Statins**

## **AIM OF THE STUDY ;**

Fibrinogen is a major determinant of plasma viscosity; an elevated fibrinogen level might also be associated with cardiovascular events.

Whether the association between fibrinogen and cardiovascular events and whether fibrinogen predicts incidence of ischemic stroke is unclear. The aim of the study is to evaluate the fibrinogen levels in 50 patients with ischemic stroke and to determine the consistency of its association when compared with 50 patients without stroke as controls.

## **MATERIALS AND METHODS;**

This study was carried out in 50 patients who were admitted in the medical intensive care unit and intermediated care unit of PSG Hospitals, Coimbatore with a diagnosis of ischemic stroke between oct 2005 and 2007.

All patients were screened according to a protocol consisting of a complete medical history, neurological examination, standardized blood tests,

CT scan of the brain or MRI, duplex scanning of the carotid arteries, and a cardiac analysis that included standard 12-lead ECG, transthoracic echocardiography and serum fibrinogen levels.

Cerebral infarction was defined as a focal neurological deficit of sudden onset that persisted beyond 24 hours in surviving patients, documented by a brain CT or an MRI indicating the presence of infarction or the absence of hemorrhage

Cerebrovascular risk factors such as never, current, or previous cigarette smoking; alcohol abuse ( $>100$  g/d); hypercholesterolemia (history of hypercholesterolemia and/or fasting total cholesterol level  $>200$  mg/dL); arterial hypertension (history of hypertension and/or systolic blood pressure  $>150$  mm Hg and/or diastolic pressure  $>90$  mm Hg); and diabetes mellitus (diagnosis according to the criteria of the National Diabetes Data Group ) were screened together with associated medical diseases, left ventricular hypertrophy (as present when documented by standard 12-lead ECG),



coronary heart disease (CHD; angina pectoris or previous Q and non-Q MI diagnosed by history, and peripheral arterial disease (PAD; in the presence of a history of intermittent claudication or previous arterial intervention or Doppler ultrasonography documentation). Routine laboratory investigations included a complete blood count, erythrocyte sedimentation rate, blood urea, creatinine, total cholesterol and glucose, electrolytes, liver enzymes, and plasma fibrinogen. Blood samples were taken within 24 to 48 hours.

Analyses were adjusted for the effects of age at screening, sex, history of hypertension, diabetes, smoking status, total cholesterol level, and body mass index.

## **EXCLUSION CRITERIA ;**

1. Major renal, hepatic, and cancerous disease;
2. Surgery or major trauma in the previous month;
3. Obvious signs and clinical evidence of acquired in-hospital infection;
4. Past history of coronary artery disease;

5. old cerebrovascular accident.

## **Determination of Plasma Fibrinogen Concentrations;**

Blood was drawn as nonfasting samples participants into citrated tubes.

Fibrinogen was measured by the clotting assay of Clauss . Mean values of

fibrinogen were 2.76 g/L in our laboratory. Blood samples from cases were

taken before administering heparin under aseptic precautions.

## **Statistical analysis ;**

It was performed using SPSS PC 11.5. Logistical regression in analysis was performed to find the effect of each variable.

**PROFORMA**

S.NO :

**Sr. FIBRINOGEN LEVELS IN ACUTE ISCHEMIC STROKE**

Name :

Age:

Address:

IP.No :

Sex:

DOA :

DOD:

**Presenting Complaints :**

**Significant Past History :**

- DM
- SHT
- IHD
- Previous MI / Stroke
- Others

**Smokes : Yes / No**

- . Cigarettes/ Beedies
- . No of Smoke : /day
- . Duration : -

**General Examination : -**

Pallor : Yes / No

Cyanosis : Yes / No

Clubbing : Yes / No

Pedal Edema : Yes / No

Vitals: - Pulse:- / min

Rhythm :- Peripheral pulses:-

BP : / mm hg

**Fundus Examintion :-**

**Carotids :-**

**Central Nervous System of Examination :-**

**Higher Mental Function :**

**Cranial Nerve**

**Motor System**

**Sensory System**

**Cerebellar**

**Others**

**Examination of other system : -**

**Investigations :-**

**CBC:**

**RBC-**

**HB -**

**WBC-**

**N , L , M , E , B**

**PLT -**

**ESR –**

**RBS -**

**UREA -**

**Sr. Creat -**

**FLP -**

**Urine Routine –**

**Sr. Fibrinogen Level :-**

**CXR :-**

**ECG :-**

**Echo :-**

**CV Doppler :-**

**CT Brain :-**

**MRI :-**

**Inference :-**

**RESULT AND ANALYSIS ;**

**Table – 1**

**SERUM FIBRINOGEN LEVEL IN STUDY SUBJECTS**

<b>NO</b>	<b>AGE</b>	<b>SEX</b>	<b>SMOKING</b>	<b>BMI</b>	<b>CHOLES</b>	<b>FIBRINOGEN in gms/l</b>
<b>1</b>	<b>57</b>	<b>F</b>		<b>24.6</b>	<b>196</b>	<b>3.82</b>
<b>2</b>	<b>43</b>	<b>F</b>		<b>22.9</b>	<b>154</b>	<b>3.57</b>
<b>3</b>	<b>64</b>	<b>M</b>	<b>YES</b>	<b>28.6</b>	<b>211</b>	<b>3.85</b>
<b>4</b>	<b>47</b>	<b>M</b>	<b>YES</b>	<b>21.4</b>	<b>254</b>	<b>4.22</b>
<b>5</b>	<b>37</b>	<b>F</b>		<b>31.4</b>	<b>290</b>	<b>3.94</b>
<b>6</b>	<b>67</b>	<b>M</b>		<b>20.6</b>	<b>174</b>	<b>4.28</b>
<b>7</b>	<b>45</b>	<b>F</b>		<b>24.8</b>	<b>118</b>	<b>3.88</b>
<b>8</b>	<b>59</b>	<b>M</b>	<b>YES</b>	<b>23.1</b>	<b>182</b>	<b>3.84</b>
<b>9</b>	<b>71</b>	<b>F</b>		<b>22.5</b>	<b>176</b>	<b>3.94</b>
<b>10</b>	<b>53</b>	<b>F</b>		<b>25.8</b>	<b>294</b>	<b>3.6</b>
<b>11</b>	<b>59</b>	<b>M</b>		<b>24.2</b>	<b>176</b>	<b>3.26</b>
<b>12</b>	<b>51</b>	<b>M</b>		<b>27.8</b>	<b>154</b>	<b>3.83</b>
<b>13</b>	<b>35</b>	<b>M</b>	<b>YES</b>	<b>22.6</b>	<b>314</b>	<b>3.93</b>
<b>14</b>	<b>61</b>	<b>F</b>		<b>23.8</b>	<b>196</b>	<b>4.02</b>

<b>15</b>	<b>54</b>	<b>M</b>		<b>26.8</b>	<b>292</b>	<b>3.6</b>
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16	64	M	YES	24.1	258	4.02
17	65	F		26.4	168	3.48
18	47	M		26.2	272	4.14
19	39	F		23.2	192	3.69
20	56	F		24.6	256	4.2
21	33	M		31.4	121	4.06
22	62	M	YES	21.7	118	3.88
23	57	F		30.2	144	3.74
24	49	M		28.4	182	4.28
25	39	F		29.6	282	3.7
26	61	F		19.6	168	4.22
27	50	M	YES	22.7	278	4.04
28	72	F		20.1	116	4.42
29	61	F		23.4	172	3.52
30	36	F		29	234	3.75
31	67	M	YES	19.3	257	3.66
32	55	F		27.4	278	3.78

33	38	F		21.8	173	4.06
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<b>34</b>	<b>58</b>	<b>M</b>	<b>YES</b>	<b>26.7</b>	<b>246</b>	<b>4.68</b>
<b>35</b>	<b>64</b>	<b>M</b>	<b>YES</b>	<b>18</b>	<b>286</b>	<b>3.9</b>
<b>36</b>	<b>68</b>	<b>F</b>		<b>26.8</b>	<b>190</b>	<b>3.54</b>
<b>37</b>	<b>40</b>	<b>M</b>		<b>23.3</b>	<b>167</b>	<b>3.58</b>
<b>38</b>	<b>61</b>	<b>F</b>		<b>32.1</b>	<b>341</b>	<b>4.86</b>
<b>39</b>	<b>58</b>	<b>F</b>		<b>20.6</b>	<b>163</b>	<b>3.92</b>
<b>40</b>	<b>51</b>	<b>M</b>		<b>28.9</b>	<b>316</b>	<b>4.52</b>
<b>41</b>	<b>69</b>	<b>F</b>		<b>21.4</b>	<b>128</b>	<b>3.32</b>
<b>42</b>	<b>39</b>	<b>F</b>		<b>27.8</b>	<b>186</b>	<b>3.81</b>
<b>43</b>	<b>53</b>	<b>M</b>		<b>24.7</b>	<b>226</b>	<b>3.76</b>
<b>44</b>	<b>63</b>	<b>F</b>		<b>22.7</b>	<b>152</b>	<b>3.12</b>
<b>45</b>	<b>70</b>	<b>M</b>	<b>YES</b>	<b>23.6</b>	<b>179</b>	<b>4.14</b>
<b>46</b>	<b>45</b>	<b>F</b>		<b>26.7</b>	<b>187</b>	<b>4.04</b>
<b>47</b>	<b>53</b>	<b>F</b>		<b>30.6</b>	<b>294</b>	<b>3.68</b>
<b>48</b>	<b>37</b>	<b>F</b>		<b>23.6</b>	<b>151</b>	<b>4.16</b>
<b>49</b>	<b>65</b>	<b>F</b>		<b>27.8</b>	<b>262</b>	<b>4.66</b>
<b>50</b>	<b>55</b>	<b>M</b>		<b>24.7</b>	<b>176</b>	<b>3.7</b>

**Table - 2**

## SERUM FIBRINOGEN LEVEL IN CONTROL GROUP

NO	AGE	SEX	SMOKING	BMI	CHOLES	FIBRINOGEN in gms/l
1	35	M	YES	23.4	186	2.94
2	39	F		24.6	265	2.68
3	39	F		30.6	294	3.14
4	36	F		26.4	157	3.02
5	34	M	YES	20.6	256	2.16
6	38	F		28.7	183	2.7
7	37	M		31.3	146	2.66
8	38	F		31.7	194	2.86
9	40	M	YES	29.1	213	2.68
10	55	F		24.8	196	3.12
11	59	M		27.4	126	2.16
12	53	F	YES	22.7	164	3.48
13	47	M		31.2	310	2.02
14	55	F		30.3	188	2.86
15	55	M		28.6	152	2.84
16	51	F	YES	22.4	272	3.76
17	48	F		21.6	164	2.28
18	57	F		27.2	282	2.58
19	52	M	YES	23.8	114	2.42
20	49	F		23.2	273	2.32



21	53	M		23.5	136	2.26
22	59	F		29.4	242	2.64
23	45	M	YES	23.3	304	3.92
24	51	M	YES	22.4	167	2.78
25	59	F		30.8	308	2.76
26	57	M	YES	24.3	297	2.88
27	60	F		24.6	174	2.14
28	56	M	YES	23.4	214	2.52
29	49	F		29.8	276	2.69
30	50	M	YES	31.2	106	2.26
31	51	F		31.4	136	2.66
32	57	M	YES	25.8	245	2.46
33	49	M	YES	23.5	264	2.58
34	67	F		24.2	192	2.92
35	70	M		25.6	289	2.7
36	63	F		22.2	174	2.58
37	65	M	YES	19.6	182	2.72
38	71	F		27.6	314	3.16
39	61	M		24	146	2.36
40	68	M		22.8	226	2.72
41	65	M	YES	22.4	212	2.78
42	61	F		18.9	278	2.26

43	61	M	YES	20.4	178	2.48
44	67	F		28.4	266	2.54
45	63	M		31.5	347	2.28
46	66	M	YES	26.6	246	4.06
47	70	F		29.2	194	2.84
48	68	M		23.4	256	2.9
49	69	F		28.2	247	2.78
50	63	M		24.1	182	2.62

**DISCUSSION ;**

Between October 2005 – 07 patients with clinical signs attributable to ischemic stroke were identified. After comprehensive evaluation, 50 patients were included.

Among 50 patients included in the derivation set there were 22 men and 28 women. The mean age was 54.06. A greater prevalence of fibrinogen level and between male sex (mean – 3.96) was noted..

The mean level of fibrinogen obtained in patients with stroke was 3.91 gms/l and the control group was 2.71 gms/l in our study. On comparing both the groups t – test was performed and the difference were found to be statistically significant. ( odds ratio – 272.332, 95% CI between 32.76 and 2263.7, p value < .001). In this study we found that serum fibrinogen level is significantly higher in patients with ischemic stroke compared to controls.

### **SERUM FIBRINIGEN LEVELS IN GMS/L IN STUDY AND CONTROL GROUP ; TABLE - III**

	TOTAL NO SUBJECTS	MEAN
STUDY GROUP	50	3.91
CONTROL GROUP	50	2.71

John Danesh et al in their meta analysis, included individual participant data from 31 prospective studies of major cardiovascular diseases and nonvascular mortality among 154211 individuals without known cardiovascular diseases at baseline. It provides the first reliable demonstration that fibrinogen is associated with the age specific incidence rates of CHD, stroke, other vascular mortality and interestingly, of the aggregate of all nonvascular causes. This meta analysis also indicates that the association of fibrinogen with CHD, stroke do not differ substantially by baseline levels of established risk factors. [160]

Sckakibara and colleagues in their study, found out that plasma fibrinogen levels are correlated with conventional cardiovascular risk factors even after adjusting for the CRP levels. [161]

**Sinning JM** et al conducted a substudy of the prospective AtheroGene registry, assessed in 1806 patients with documented CAD and stable angina pectoris, the risk of cardiovascular death and non-fatal myocardial infarction (n=183) over a median follow-up of 3.5 (maximum 7.7) years according to baseline levels of C-reactive protein and fibrinogen and found out that in patients with documented CAD, C-reactive protein and fibrinogen were predictive for future cardiovascular risk. [161]

In one study conducted in 2632 subjects from cycle 5 of Framingham offspring population further characterize the association between fibrinogen and cardiovascular disease. [163]

Schila sabeti and colleagues assessed serum fibrinogen levels without recent cerebrovascular diseases in 1268 patients, found that although fibrinogen cannot be referred to as an independent risk predictor, it still may be worth considering as an indicator for progressive atherosclerosis and potentially for the occurrence of future neurological complications. [164]

Large population based studies such as COPENHAGEN CITY STUDY ( n = 8755 ) and the GOTHENBURG study ( n = 792 ) unequivocally demonstrated an increasing risk for stroke with increasing levels of fibrinogen, suggesting that fibrinogen may be worth investigating further with respect to its role in cerebrovascular disease.

EUROSTROKE is a collaborative project among ongoing European cohort studies. This analysis on the Eurostroke project indicates that fibrinogen is a powerful indicator for stroke.

In the Leigh General Practice Study, 505 men aged 40–69 years and free from IHD, diabetes and hypertension were recruited from one general practice in the UK. After a mean follow-up of 7.3 years, 40 cases of MI occurred. On multivariate analysis, plasma fibrinogen proved to be the strongest predictor of adverse cardiovascular events

One more prospective trial for 13.5 yrs conducted by wilhelmsen and colleagues proved the possibility of serum fibrinogen to play an important part

in the development of stroke and MI.

However there have been few studies which demonstrated no relation between serum fibrinogen levels and stroke, to quote a few studies...

Peter M . Rothudi et al estimated fibrinogen concentration and risk of ischemic stroke and acute coronary events in 5113 patients and concluded there was no significant heterogeneity in fibrinogen risk associations.

Schinichi sabo et al studied the association of serum fibrinogen concentration with stroke in 4608 men and 7589 women and did not find a positive association between fibrinogen and risk of ischemic stroke. [165]

This finding was consistent with the result of ARIC study showing a positive association of fibrinogen with risk of coronary heart disease but not of ischemic stroke.

However to find out in totality whether serum fibrinogen is an independent risk factor or not, many studies with large number of subjects with proper inclusion and exclusion criteria will have to be conducted to come

to a final definite conclusion.

In our study there is a positive correlation between fibrinogen levels and smoking was found out. Similar data are available from epidemiological studies. In the Framingham study, plasma fibrinogen values were significantly higher in smokers than in non-smokers, with a dose-dependent increase with smoking in both sexes; ex-smokers had values as low as those of non-smokers.

In the second MONICA Augsburg survey, the impact on the population plasma fibrinogen level was most pronounced for age in both sexes, followed closely by body mass index and cigarette smoking [51]. In the MUNSTER Heart Study, smoking-related adverse changes in plasma fibrinogen were of greater magnitude in men than in women [102]. A switch from cigarette to cigar smoking is also associated with a large increase in plasma fibrinogen levels [103], in keeping with the observation that cigar smokers remain at an increased risk of IHD [104].

But there is no significant two way interaction between fibrinogen and



two other risk factors, serum total cholesterol and BMI in our study. ( $p > .001$ ). Baseline total cholesterol and body mass index were compared in cases and controls. Mean total cholesterol level was lower in cases than in controls. And there was no significant relationship between total cholesterol and the risk of ischemic stroke in this study. (95% CI .991-101.004).

Carrole L Hart et al analysed all the risk factors for stroke using 7052 men and 8354 women prospectively for 20 years. In this study it was found to be no relationship between total cholesterol and stroke.[166]

Tom hoslen in his study found out that a higher cholesterol favours development of minor strokes and major strokes are often seen in patients with lower cholesterol levels.

The role of cholesterol in stroke is unclear. Most prospective studies have failed to find a definite relation between total cholesterol level and the risk of stroke. This finding is consistent with the findings from the Copenhagen Study

[167]. Despite the lack of association between serum total cholesterol and risk of stroke in observational epidemiological studies, the results of lipid-lowering trials with statin agents suggest benefit for stroke reduction [168-170]. It has been suggested that the beneficial effects of statins on clinical events may involve mechanisms independent of lipid-lowering such as modification of endothelial function, inflammatory responses, plaque stability, and thrombus formation. [171]

Encouragingly, plasma fibrinogen is partly a modifiable risk factor, and suitable lifestyle changes usually result in favourable decreases in plasma fibrinogen levels, although drug therapy has not been fully validated. In one trial conducted by M. Lin et al included five trials involving 2926 patients, and found out that fibrinogen depleting agents moderately reduce the proportion of patients who were dead or disabled. Several drugs are known to reduce the fibrinogen levels, including bezafibrate, beta blockers, pentoxifylline and ticlopidine [172,173]. Moreover lifestyle modification, including smoking

cessation and increased exercise can reduce fibrinogen levels. [174]. However more data, particularly ESTAT data, are needed before more reliable conclusions can be drawn.

## **SUMMARY AND CONCLUSION ;**

This study was carried out on 50 subjects who presented with ischemic stroke and got admitted in the medical intensive care unit between oct 2005 – 07. Serum fibrinogen level was estimated by using clauss method.

The mean level of fibrinogen obtained in patients with stroke was 3.91 gms/l and the control group was 2.71 gms/l in our study. In this study we found that serum fibrinogen level is significantly higher in patients with ischemic stroke compared to controls. . ( odds ratio – 272.332, 95% CI between 32.76 and 2263.7, p value < .001). Serum fibrinogen level in this study was found to be an important risk factor in ischemic stroke.

Literature review in connection with the study revealed many studies which demonstrated the independent effects of increased fibrinogen level as one of the risk factor for ischemic stroke.

A definite association exists between fibrinogen and atherothrombogenesis. However, the nature of the link is unclear. Although epidemiological and clinical studies suggest that the link is causal, no definite

evidence exists. It appears that fibrinogen concentration and plasma viscosity are at least as predictive of coronary events as are cholesterol concentration, diastolic blood pressure and body mass index.

Encouragingly, plasma fibrinogen is partly a modifiable risk factor, and suitable lifestyle changes usually result in favourable decreases in plasma fibrinogen levels, although drug therapy has not been fully validated.

The relationship between genetic polymorphism in the fibrinogen gene and cardiovascular risk is very complex. Although polymorphisms in the fibrinogen gene could potentially augment the cardiovascular risk through increased fibrinogen levels, the effect appears to be antagonized by some unknown mechanism due to the same polymorphism. Therefore, polymorphisms of fibrinogen gene may modify the effect of external influences on the final phenotype (i.e. the vascular risk) rather than directly affecting the risk of the disease through plasma fibrinogen levels. In future, gene-environment interactions should be considered in evaluating the relevance of genetic variations on the risk of cardiovascular disease

Future directions require determination of the 'critically elevated' fibrinogen threshold value, development of drugs that would specifically and

safely decrease plasma fibrinogen levels and conduction of interventional trials to study the influence of lowering fibrinogen levels on overall cardiovascular risk profile.

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